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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SPW99.07	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/09116	International filing date (day/month/year) 15/09/2000	Priority date (day/month/year) 16/09/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant SOLVAY PHARMACEUTICALS B.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 19/03/2001	Date of completion of this report 08.01.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer SCHEFFZYK, I Telephone No. +49 89 2399 8602 

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International application No. PCT/EP00/09116

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-33 as originally filed

Claims, No.:

1-24 as received on 30/10/2001 with letter of 26/10/2001

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-6, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 17,20,22 completely and 16 partially.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 17,20,22 completely and 16 partially .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

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citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5,13-16,18,19,21,24
	No:	Claims	6-12,23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16,18,19,21,23,24,
Industrial applicability (IA)	Yes:	Claims	1-15,19,21, 23
	No:	Claims	16,18,24

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION V-----

With respect to claim 6 it is noted that the term "capable of" does not necessarily require the presence of a nucleotide sequence encoding IGS3 within the expression vector but only requires that if such a sequence is present then the expression vector must have means which renders the vector capable of producing the IGS3 polypeptide. Hence, according to the present wording of claim 6 said claim may be directed to expression vectors as such. Correspondingly, novelty of claims 6-12 cannot be acknowledged.

With respect to claims 10-12 it is further noted that in the absence of a specific sequence the term "ISG3" only is an internal designation without any well-recognized technical meaning to a person skilled in the art. Correspondingly, it is completely meaningless for the interpretation of the scope of these claims. Relating to this it is pointed out that a claim must be clear when seen alone, i.e. without the context of the specification. However, for the sake of completeness, it is noted that even in the light of the definition given in present application on page 7, line 21 the meaning of said term remains obscure due to the alternative "variant thereof". Correspondingly, claim 10 relates to any receptor membrane preparation derived from any cell, claims 11 and 12 relate to any process for producing a polypeptide and claim 23 to any host cell

To sum up: claims 6-12 and 23 do not meet the requirements of Art. 33(2) PCT.

The inventors of present application merely assume based on sequence alignments that SEQ.ID.NO. 2 is a new member of the family of the G-protein coupled receptors (see page 14 of present application, line 12 "...are expected to have..."). However, present application fails to provide facts and data showing evidence for said "educated guess". In the absence of such evidence, however, the presence of an inventive step cannot be acknowledged (Art. 33(3) PCT) since the mere provision of a

sequence without the function thereof is not considered to be inventive. In addition, without a specific function of a claimed sequence industrial applicability thereof also is questionable (Art. 33(4) PCT).

SECTION VII-----

- 1). Concerning claim 1(b) it is noted that a deposit receipt should be submitted (pages 34-37 of present application relate to the claims but not to deposit receipts?!)
- 2). Claim 7 should be checked: it seems to be more appropriate that said claim is directed to an expression vector containing a nucleic acid according to claim 1.
- 3). No basis can be found in the application as filed for the amendment made in claim 15, i.e. an antibody immunospecific for a variant of SEQ.ID.NO.2. (Art. 34(2)(b) PCT.) The same applies correspondingly to the amendment made in claim 16 "suffering from a disease related to expression or activity of the IGS3 polypeptide receptor".
However, nevertheless, concerning claim 16 it is noted that in case the Applicant can show a basis for said amendment novelty could not be acknowledged since antibodies directed against variants of SEQ.ID.NO. 2 certainly would not be novel over readily available antibodies directed against known G-protein coupled receptors.

SECTION VIII-----

- 1). Claim 16 lacks technical support by present specification since the application does not show the suitability of presently claimed polypeptide for medical purposes.
- 2). In addition, claim 16 lacks clarity since it does not recite a specific disorder to be treated.

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- 3). Moreover, in so far as present application fails to teach an agonist claim 21 lacks technical support (Art. 5 and 6 PCT).
- 4). Claims 16, 18 and 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims

- replaced by
Article 34
1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:
 - 5 a) a nucleotide sequence encoding the IGS3 polypeptide according to SEQ ID NO: 2;
 - b) a nucleotide sequence encoding the polypeptide encoded by the DNA insert contained in the deposit no. CBS 102196 at the Centraalbureau voor Schimmelcultures at Baarn (The Netherlands), in particular a nucleotide sequence corresponding to the SEQ ID NO: 1;
 - 10 c) a nucleotide sequence having at least 80 % (preferably at least 90%) sequence identity over its entire length to the nucleotide sequence of (a) or (b);
 - d) a nucleotide sequence which is complimentary to the nucleotide sequence of (a) or (b) or (c).
 - 15 2. The polynucleotide of claim 1 wherein said polynucleotide comprises the nucleotide sequence contained in SEQ ID NO:1 encoding the IGS3 polypeptide of SEQ ID NO:2.
 3. The polynucleotide of claim 1 wherein said polynucleotide comprises a nucleotide sequence that is at least 80% identical to that of SEQ ID NO:1 over its entire length.
 - 20 4. The polynucleotide of claim 3 which is the polynucleotide of SEQ ID NO:1.
 5. The polynucleotide of claim 1-4 which is DNA or RNA.
 - 25 6. A hybridization probe comprising the polynucleotide of claim 1 or a fragment thereof of at least 5 nucleotides and preferably between 30 and 50 nucleotides.
 7. A DNA or RNA molecule comprising an expression system, wherein said expression system is capable of producing an IGS3 polypeptide comprising an amino acid sequence, which has at least 80% identity with the polypeptide of SEQ ID NO:2 when said expression system is present in a compatible host cell.
 - 30 8. A host cell comprising the expression system of claim 7.
 - 35 9. A host cell according to claim 8 which is a yeast cell

10. A host cell according to claim 8 which is an animal cell
11. IGS3 receptor membrane preparation derived from a cell according to claim 8-10.
- 5 12. A process for producing an IGS3 polypeptide comprising culturing a host of claim 8 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture.
- 10 13. A process for producing a cell which produces an IGS3 polypeptide thereof comprising transforming or transfecting a cell with the expression system of claim 7 such that the cell, under appropriate culture conditions, is capable of producing an IGS3 polypeptide.
14. An IGS3 polypeptide comprising an amino acid sequence which is at least 80% identical to the amino acid sequence of SEQ ID NO:2 over its entire length.
- 15 15. The polypeptide of claim 14 which comprises the amino acid sequence of SEQ ID NO:2.
16. An antibody immunospecific for the IGS3 polypeptide of claim 14.
- 20 17. A method for the treatment of a subject in need of enhanced activity or expression of IGS3 polypeptide receptor of claim 14 comprising:
- (a) administering to the subject a therapeutically effective amount of an agonist to said receptor; and/or
- 25 (b) providing to the subject an isolated polynucleotide comprising a nucleotide sequence that has at least 80% identity to a nucleotide sequence encoding the IGS3 polypeptide of SEQ ID NO:2 over its entire length; or a nucleotide sequence complementary to said nucleotide sequence in a form so as to effect production of said receptor activity in vivo.
- 30 18. A method for the treatment of a subject having need to inhibit activity or expression of IGS3 polypeptide receptor of claim 14 comprising:
- (a) administering to the subject a therapeutically effective amount of an antagonist to said receptor; and/or
- 35 (b) administering to the subject a polynucleotide that inhibits the expression of the nucleotide sequence encoding said receptor; and/or

- (c) administering to the subject a therapeutically effective amount of a polypeptide that competes with said receptor for its ligand.

- 5 19. A process for diagnosing a disease or a susceptibility to a disease in a subject related to expression or activity of the IGS3 polypeptide of claim 14 in a subject comprising:
- (a) determining the presence or absence of a mutation in the nucleotide sequence encoding said IGS3 polypeptide in the genome of said subject; and/or
- (b) analyzing for the presence or amount of the IGS3 polypeptide expression in a sample derived from said subject.
- 10 20. A method for identifying agonists to the IGS3 polypeptide of claim 14 comprising:
- (a) contacting a cell which produces a IGS3 polypeptide with a test compound; and
- (b) determining whether the test compound effects a signal generated by activation of the IGS3 polypeptide.
- 15 21. An agonist identified by the method of claim 20.
22. A method for identifying antagonists to the IGS3 polypeptide of claim 14 comprising:
- (a) contacting a cell which produces a IGS3 polypeptide with an agonist; and
- 20 (b) determining whether the signal generated by said agonist is diminished in the presence of a candidate compound.
23. An antagonist identified by the method of claim 22.
- 25 24. A recombinant host cell produced by a method of claim 13 or a membrane thereof expressing an IGS3 polypeptide.
25. A method of creating a genetically modified non-human animal comprising the steps of:
- 30 a) ligating the coding portion of a polynucleotide consisting essentially of a nucleic acid sequence encoding a protein having the amino acid sequence SEQ ID NO: 2 or a biologically active fragment thereof to a regulatory sequence which is capable of driving high level gene expression or expression in a cell type in which the gene is not normally expressed in said animal; or
- b) engineering the coding portion of a polynucleotide consisting essentially of a nucleic acid sequence encoding a protein having the amino acid sequence SEQ ID NO: 2 or a biologically active fragment thereof and reintroducing said sequence in the genome of said animal in such a way that the endogenous
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gene alleles encoding a protein having the amino acid sequence SEQ ID NO: 2 or a biologically active fragment are fully or partially inactivated.